

1645
IDS

Please type a plus sign (+) inside this box →

**TRANSMITTAL
FORM**

(to be used for all correspondence after initial filing)

Application Number	09/611,419
Filing Date	July 6, 2000
First Named Inventor	Smith et al.
Group Art Unit	1645
Examiner Name	TBA
Attorney Docket Number	A33626 067252.0105

Total Number of Pages in This Submission

ENCLOSURES (check all that apply)

- ☐ Fee Transmittal Form
- ☐ Fee Attached
- ☐ Amendment / Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☒ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53

- ☐ Assignment Papers (for an Application)
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____

- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please identify below):
Form 1449 and 125 documents in seven (7) bound volumes

Remarks

☐**SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT**Firm
or
Individual nameBakerBotts LLP
30 Rockefeller Plaza
New York, NY 10112

Signature

Att Name: Rochelle K. Seide
PTO Reg: 32,300

Date

April 26, 2002

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date: April 26, 2002

Typed or printed name

Rochelle K. Seide

Signature

Date

April 26, 2002

MAY 03 2002

RECEIVED

TECH CENTER 1600/2000

RECEIVED

MAY 03 2002

TECH CENTER 1600/2900

BAKER BOTTS LLP

MAY 01 2002

TRADEMARK OFFICE

FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT

(\$ 0)

Complete if Known

Application Number	09/611,419
Filing Date	July 6, 2000
First Named Inventor	Smith et al.
Examiner Name	TBA
Group Art Unit	1645
Attorney Docket No.	A33626 067252.0105

METHOD OF PAYMENT

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit
Account
Number

02-4377

Deposit
Account
Name

Baker Botts LLP

- ☒ Charge Any Additional Fee Required
Under 37 CFR 1.16 and 1.17

- ☐ Applicant claims small entity status.
See 37 CFR 1.27

2. ☐ Payment Enclosed:

☐ Check ☐ Credit card ☐ Money
Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Small Entity

Fee (\$)	Fee (\$)	Fee Description	Fee Paid
740	370	Utility filing fee	
330	165	Design filing fee	
510	255	Plant filing fee	
740	370	Reissue filing fee	
160	80	Provisional filing fee	

SUBTOTAL (1) (\$ 0)

2. EXTRA CLAIM FEES

Total Claims	Extra Claims	Fee from below	Fee Paid	
20**	= 0	X	= 0	
Independent Claims	3**	= 0	X	= 0
Multiple Dependent				

Large Entity Small Entity

Fee (\$)	Fee (\$)	Fee Description
18	9	Claims in excess of 20
84	42	Independent claims in excess of 3
280	140	Multiple dependent claim, if not paid
84	42	** Reissue independent claims over original patent
18	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2)

(\$ 0)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee (\$)	Small Entity Fee (\$)	Fee Description	Fee Paid
130	65	Surcharge - late filing fee or oath	
50	25	Surcharge - late provisional filing fee or cover sheet	
130	130	Non-English specification	
2,520	2,520	For filing a request for <i>ex parte</i> reexamination	
920*	920*	Requesting publication of SIR prior to Examiner action	
1,840*	1,840*	Requesting publication of SIR after Examiner action	
110	55	Extension for reply within first month	
400	200	Extension for reply within second month	
920	460	Extension for reply within third month	
1,440	720	Extension for reply within fourth month	
1,960	980	Extension for reply within fifth month	
320	160	Notice of Appeal	
320	160	Filing a brief in support of an appeal	
280	140	Request for oral hearing	
1,510	1,510	Petition to institute a public use proceeding	
110	55	Petition to revive - unavoidable	
1,280	640	Petition to revive - unintentional	
1,280	640	Utility issue fee (or reissue)	
460	230	Design issue fee	
620	310	Plant issue fee	
130	130	Petitions to the Commissioner	
50	50	Processing fee under 37 CFR 1.17(q)	
180	180	Submission of Information Disclosure Stmt	
40	40	Recording each patent assignment per property (times number of properties)	
740	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
740	370	For each additional invention to be examined (37 CFR § 1.129(b))	
740	370	Request for Continued Examination (RCE)	
900	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$ 0)

SUBMITTED BY

Name (Print/Type)

Rochelle K. Seide

Registration No.
(Attorney/Agent)

32,300

Complete (if applicable)

Telephone

(212) 408-2626

Signature

Rochelle K. Seide

Date

April 26, 2002

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

BAKER BOTTS LLP

Attorney Docket Number: A33626 067252.0105

Title: RECOMBINANT VACCINE AGAINST BOTULINUM NEUROTOXIN



Use Space Below for Additional Information:



A33626 067252.0105
PATENT

TECH CENTER 1600/2900

MAY 03 2002

RECEIVED

Applicant : Smith et al.
Serial No. : 09/611,419 Examiner : Portner, V.
Filed : July 6, 2000 Group Art Unit : 1645
For : RECOMBINANT VACCINE AGAINST BOTULINUM NEUROTOXIN

INFORMATION DISCLOSURE STATEMENT

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231

April 26, 2002
Date of Deposit

Rochelle K. Seide
Attorney Name

Rochelle K. Seide
Signature

32,300
PTO Registration No.

April 26, 2002
Date of Signature

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

In accordance with 37 C.F.R. § 1.56, Applicants respectfully request that the documents relating to the above-mentioned application listed herein in reverse chronological alphabetical order be considered and made of record in the U.S. Patent and Trademark Office.

VOLUME 1

1. Ahmed SA et al., 2001, "Enzymatic autocatalysis of botulinum A neurotoxin light chain" *J. Protein Chem.* **20**(3):221–231;
2. Schmidt JJ et al., 2001, "High-throughput assays for botulinum neurotoxin proteolytic activity: serotypes A, B, D, and F" *Analytical Biochemistry* **296**:130–137;
3. URL:<http://www.cdc.gov/ncidod/srp/drugservice/immuodrugs.htm>, 2001, "Immunobiologic Agents and Drugs Available from the Centers for Disease Control. Descriptions, Recommendations, Adverse Reactions and Serologic Response" Centers for Disease Control, Atlanta, GA;
4. Ahmed SA et al., 2000, "Light chain of botulinum A neurotoxin expressed as an inclusion body from a synthetic gene is catalytically and functionally active" *J. Protein Chem.* **19**(6):475–487;
5. Alderton JM et al., 2000, "Evidence for a vesicle-mediated maintenance of store-operated calcium channels in a human embryonic kidney cell line" *Cell. Calcium* **28**(3):161–169;
6. Byrne MP et al., 2000, "Fermentation, purification, and efficacy of a recombinant vaccine candidate against botulinum neurotoxin type F from *Pichia pastoris*" *Protein Expr Purif.* **18**(3):327–337;
7. Dalbey RE et al., 2000, "Evolutionarily related insertion pathways of bacterial, mitochondrial, and thylakoid membrane proteins" *Annu. Rev. Cell Dev. Biol.* **16**:51–87;
8. Ettinger RA et al., 2000, "Beta 57-Asp plays an essential role in the unique SDS stability of HLA-DQA1*0102/DQB1*0602 alpha beta protein dimer, the class II MHC allele associated with protection from insulin-dependent diabetes mellitus" *J. Immunol* **165**:3232–3238;
9. Kadkhodayan S et al., 2000, "Cloning, expression, and one-step purification of the minimal essential domain of the light chain of botulinum neurotoxin type A" *Protein Expr. Purif.* **19**(1):125–130;
10. Knapp M et al., 2000, "The crystal structure of botulinum toxin A zinc protease domain." Presented at the 37th Annual Meeting of the Interagency Botulinum Research Coordinating Committee, October 17–20, 2000, Alisomar, California;
11. Li L et al., 2000, "Role of zinc binding in type A botulinum neurotoxin light chain's toxic structure" *Biochemistry* **39**:10581–10586;
12. Smith LA et al., WO 00/67700 published November 16, 2000;
13. Strasser A et al., 2000, "Apoptosis signaling" *Annu. Rev. Biochem* **69**:217–245;

14. Cai S et al., 1999, "Enhancement of the endopeptidase activity of botulinum neurotoxin by its associated proteins and dithiothreitol" *Biochemistry* **38**:6903–6910;
15. Claiborne A et al., 1999, "Protein-sulfenic acids: diverse roles for an unlikely player in enzyme catalysis and redox regulation" *Biochemistry* **38**:15407–15416;

VOLUME 2

16. Lacy DB et al., 1999, "Sequence homology and structural analysis of the clostridial neurotoxins" *J. Mol. Biol.* **291**:1091–1104;
17. Li L et al., 1999, "High-level expression, purification, and characterization of recombinant type A botulinum neurotoxin light chain" *Protein Expr. Purif.* **17**:339–344;
18. Li L et al., 1999, "In vitro translation of type A Clostridium botulinum neurotoxin heavy chain and analysis of its binding to rat synaptosomes" *J Protein Chem.* **18**(1):89-95;
19. Williams JA, U.S. Pat. No. 5,919,665 issued July 6, 1999;
20. Byrne MP et al., 1998, "Purification, Potency, and Efficacy of the Botulinum Neurotoxin Type A Binding Domain from *Pichia pastoris* as a Recombinant Vaccine Candidate," *Infect. Immun.* **66**:4817-4822;
21. Fu F et al., 1998, "Role of zinc in the structure and toxic activity of botulinum neurotoxin" *Biochemistry* **37**:5267–5278;
22. Lacy DB et al., 1998, "Crystal Structure of Botulinum Neurotoxin Type A and Implications for Toxicity," *Nat. Struct. Biol.* **5**:898-902;
23. Nowakowski JL et al., 1998, "Production of an expression system for a synaptobrevin fragment to monitor cleavage by botulinum neurotoxin B" *J. Protein Chem.* **17**:453–462;
24. Potter KJ et al., 1998, "Production and purification of the heavy-chain fragment C of botulinum neurotoxin, serotype B, expressed in the methylotrophic yeast *Pichia pastoris*" *Protein Expr Purif.* **13**(3):357-365;
25. Schmidt JJ et al., 1998, "Type A botulinum neurotoxin proteolytic activity: development of competitive inhibitors and implications for substrate specificity at the S1' binding subsite" *FEBS Lett.* **435**:61–64;
26. Smith LA, 1998, "Development of recombinant vaccines for botulinum neurotoxin" *Toxicon.* **36**(11):1539-48;

VOLUME 3

27. Williams JA, WO 98/08540 published March 5, 1998;

VOLUME 4

28. Adler M et al., 1997, "Protection by the heavy metal chelator N,N,N',N'-tetrakis (2-pyridylmethyl)ethylenediamine (TPEN) against the lethal action of botulinum neurotoxin A and B" *Toxicon* **35**:1089-1100;
29. Brown DR et al., 1997, "Identification and Characterization of a Neutralizing Monoclonal Antibody Against Botulinum Neurotoxin, Serotype F, Following Vaccination with Active Toxin," *Hybridoma*, **16**:447-456;
30. Chen F et al., 1997, "Antibody mapping to domains of botulinum neurotoxin serotype A in the complexed and uncomplexed forms" *Infect. Immun.* **65**:1626-1630;
31. Chiruvolu V et al., 1997, "Recombinant Protein Expression in an Alcohol Oxidase-Defective Strain of *Pichia pastoris* in Feed-Batch Fermentations, *Enzyme Microbiol. Technol.* **21**:277-283;
32. Kiyatkin N et al., 1997, "Induction of an immune response by oral administration of recombinant botulinum toxin" *Infect. Immun.* **65**:4586-4591;
33. Lebeda FJ et al., 1997, "Predicting Differential Antigen-Antibody Contact Regions Based on Solvent Accessibility," *J. Protein Chem.* **16**:607-618;
34. Schmidt JJ et al., 1997, "Endoprotease activity of type A botulinum neurotoxin: substrate requirements and activation by serum albumin" *J. Protein Chem.* **16**(1):19-26;
35. Sheridan RE et al., 1997, "Structural features of aminoquinolines necessary for antagonist activity against botulinum neurotoxin" *Toxicon* **35**:1439-1451;
36. Washbourne P et al., 1997, "Botulinum neurotoxin types A and E require the SNARE motif in SNAP-25 for proteolysis" *FEBS Lett.* **418**:1-5;
37. Williams JA et al., U.S. Pat. No. 5,601,823 issued February 11, 1997;
38. Dertzbaugh MT et al., 1996, "Mapping of protective and cross-reactive domains of the type A neurotoxin of *Clostridium botulinum*" *Vaccine* **14**:1538-1544;
39. Foran P et al., 1996, "Botulinum neurotoxin C1 cleaves both syntaxin and SNAP-25 in intact and permeabilized chromaffin cells: correlation with its blockade of catecholamine release" *Biochemistry* **35**:2630-2636;

40. Auld DS, 1995, "Removal and replacement of metal ions in metallopeptidases" *Meth. Enzymol.* **248**:228-242;
41. Bi GQ et al., 1995, "Calcium-regulated exocytosis is required for cell membrane resealing" *J. Cell Biol.* **131**:1747-1758;
42. Cardoso F et al., 1995, "Clinical use of botulinum neurotoxins". In *Current Topics in Microbiology and Immunology* (Capron A et al., eds.), Springer-Verlag, Germany, **195**:123-141;
43. Clayton MA et al., 1995, "Protective vaccination with a recombinant fragment of Clostridium botulinum neurotoxin serotype A expressed from a synthetic gene in Escherichia coli" *Infect Immun.* **63**(7):2738-2742;
44. Klatt P et al., 1995, "Structural analysis of porcine brain nitric oxide synthase reveals a role for tetrahydrobiopterin and L-arginine in the formation of an SDS-resistant dimer" *EMBO J.* **14**:3687-3695;
45. LaPenotiere HF et al., 1995, "Expression of a large, nontoxic fragment of botulinum neurotoxin serotype A and its use as an immunogen" *Toxicon.* **33**(10):1383-1386;
46. Montecucco C et al., 1995, "Structure and function of tetanus and botulinum neurotoxins" *Q. Rev. Biophys.* **28**:423-472;
47. Oguma K et al., 1995, "Structure and Function of Clostridium botulinum Toxins" *Microbiol. Immunol.* **39**:161-168;
48. Pace CN et al., 1995, "How to measure and predict the molar absorption coefficient of a protein" *Protein Sci.* **4**:2411-2423;

VOLUME 5

49. Romanos MA et al., 1995, "Expression of Cloned Genes in Yeast," *DNA Cloning 2: Expression Systems*, (Glover D., et al., Eds.), Oxford Univ. Press, London, pp. 123-167;
50. Schiavo G et al., 1995, "Intracellular targets and metalloprotease activity of tetanus and botulinum neurotoxins." In *Clostridial Neurotoxins: The Molecular Pathogenesis of Tetanus and Botulism* (Montecucco, C., ed.), Springer, New York, pp. 257-273;
51. Schmidt JJ et al., 1995, "Proteolysis of synthetic peptides by type A botulinum neurotoxin" *J. Protein Chem.* **14**(8):703-708;
52. Shone CC et al., 1995, "Growth of clostridia and preparation of their neurotoxins" *Curr. Top. Microbiol. Immunol.* **195**:143-160;

53. Zhou L et al., 1995, "Expression and purification of the light chain of botulinum neurotoxin A: a single mutation abolishes its cleavage of SNAP-25 and neurotoxicity after reconstitution with the heavy chain" *Biochemistry* **34**(46):15175–15181;
54. Foran P et al., 1994, "Differences in the protease activities of tetanus and botulinum B toxins revealed by the cleavage of vesicle-associated membrane protein and various sized fragments" *Biochemistry* **33**:15365–15374;
55. Krieglstein KG et al., 1994, "Covalent structure of botulinum neurotoxin type A: location of sulfhydryl groups, and disulfide bridges and identification of C-termini of light and heavy chains" *J. Protein Chem.* **13**:49-57;
56. Lebeda FJ et al.:1994, "Secondary structural predictions for the clostridial neurotoxins" *Proteins* **20**:293–300;
57. Li Y et al., 1994, "A single mutation in the recombinant light chain of tetanus toxin abolishes its proteolytic activity and removes the toxicity seen after reconstitution with native heavy chain" *Biochemistry* **33**:7014–7020;
58. Montecucco C et al., 1994, "Mechanism of action of tetanus and botulinum neurotoxins" *Mol. Microbiol* **13**:1–8;
59. Nishiki TI et al., 1994, "Identification of Protein Receptor for *Clostridium botulinum* Type B Neurotoxin in Rat Brain Synaptosomes" *J. Biol. Chem.* **269**:10498-10503;
60. Rossetto O et al., 1994, "SNARE motif and neurotoxins" *Nature* **372**:415–416;
61. Schiavo G et al., 1994, "Botulinum G neurotoxin cleaves VAMP/synaptobrevin at a single Ala-Ala peptide bond" *J. Biol. Chem.* **269**:20213–20216;
62. Scorer CA et al., 1994, "Rapid Selection Using G418 of High Copy Number Transformants of *Pichia pastoris* for High-Level Foreign Gene Expression," *Bio/Technology*, **12**:181-184;
63. Shone CC et al., 1994, "Peptide substrate specificity and properties of the zinc-endopeptidase activity of botulinum type B neurotoxin" *Eur. J. Biochem.* **225**:263–270;
64. Steinhardt RA et al., 1994, "Cell membrane resealing by a vesicular mechanism similar to neurotransmitter release" *Science* **263**:390–393;
65. Baltz RH et al., eds., 1993, *Industrial Microorganisms: Basic and Applied Molecular Genetics*, American Society for Microbiology, Washington, D.C., pp. 122-126;
66. Blasi J et al., 1993, "Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25" *Nature* **365**:160–163;

67. Campbell KD et al., 1993, "Gene probes for identification of the botulinal neurotoxin gene and specific identification of neurotoxin types B, E, and F" *J Clin Microbiol.* **31**(9):2255-2262;
68. Carroll SB, U.S. Pat. No. 5,196,193 issued March 23, 1993;
69. Cregg JM et al., 1993, "Recent Advances in the Expression of Foreign Genes in *Pichia pastoris*," *Bio/Technology*, **11**:905-910;
70. de Paiva A et al., 1993, "A role for the interchain disulfide or its participating thiols in the internalization of botulinum neurotoxin A revealed by a toxin derivative that binds to ecto-acceptors and inhibits transmitter release intracellularly" *J. Biol. Chem.* **268**:20838-20844;
71. Dertzbaugh M et al., May 1993, "Cloning and Expression of Peptides derived from the botulinum neurotoxin serotype A gene" 93rd American Society for Microbiology General Meeting, Atlanta, GA, Session 334, E-105, p.161;
72. Gimenez JA et al., 1993, "Botulinum Type A neurotoxin digested with pepsin yields 132, 97, 72, 45, 42, and 18 kD fragments" *J Protein Chem.* **12**(3):351-363;
73. LaPenotiere HF et al., 1993, "Development of a molecular engineered vaccine for C. botulinum neurotoxins" in *Botulinum and Tetanus Toxins* (DasGupta BR, ed.) Plenum Press, New York;
74. Schiavo G et al., 1993, "Identification of the Nerve Terminal Targets of Botulinum Neurotoxin Serotypes A, D, and E" *J. Biol. Chem.* **268**:23784-23787;
75. Shone CC et al., 1993, "Proteolytic Cleavage of Synthetic Fragments of Vesicle-Associated Membrane Protein, Isoform-2 by Botulinum Type B Neurotoxin" *Eur. J. Biochem.* **217**:965-971;
76. Simpson LL et al., 1993, "Chelation of zinc antagonizes the neuromuscular blocking properties of the seven serotypes of botulinum neurotoxin as well as tetanus toxin" *J. Pharmacol. Exp. Ther.* **267**:720-727;

VOLUME 6

77. Sreekrishna K, 1993, "Strategies for Optimizing Protein Expression and Secretion in the Methylotrophic Yeast *Pichia pastoris*," *Industrial Microorganisms: Basic and Applied Molecular Genetics*, Baltz, R. H., et al, Eds.), pp. 119-126, Am. Soc. Microbiol., Washington, DC;

78. Ahmed SA et al., 1992, "Active-site structural comparison of streptococcal NADH peroxidase and NADH oxidase. Reconstitution with artificial flavins" *J. Biol. Chem.* **267**:3832-3840;
79. Kurazono H et al., 1992, "Minimal essential domains specifying toxicity of the light chains of tetanus toxin and botulinum neurotoxin type A" *J Biol Chem.* **267**(21):14721-14729;
80. Montal MS et al., 1992, "Identification of an Ion Channel-Forming Motif in the Primary Structure of Tetanus and Botulinum Neurotoxins" *FEBS* **313**:12-18;
81. Romanos MA et al., 1992, "Foreign Gene Expression in Yeast: A Review," *Yeast*, **8**:423-488;
82. Schiavo G et al., 1992, "Tetanus and Botulinum-B Neurotoxins Block Neurotransmitter Release by Proteolytic Cleavage of Synaptobrevin" *Nature* **359**:832-835;
83. Schiavo G et al., 1992, "Tetanus Toxin is a Zinc Protein and its Inhibition of Neurotransmitter Release and Protease Activity Depend on Zinc" *EMBO J.* **11**:3577-3583;
84. Whelan SM et al., 1992, "Molecular cloning of the Clostridium botulinum structural gene encoding the type B neurotoxin and determination of its entire nucleotide sequence" *Appl. Environ. Microbiol.* **58**:2345-2354;
85. Clare JJ et al., 1991, "High-Level Expression of Tetanus Toxin Fragment C in *Pichia pastoris* Strains Containing Multiple Tandem Integrations of the Gene," *Bio/Technology* **9**:455-460;
86. Niemann H et al., 1991, "Clostridial neurotoxins: from toxins to therapeutic tools?" *Behring Inst Mitt.* **89**:153-162;
87. Poulain B et al., 1991, "Heterologous Combinations of Heavy and Light Chains from Botulinum Neurotoxin A and Tetanus Toxin Inhibit Neurotransmitter Release in *Aplysia*" *J. Biol. Chem.* **266**:9580-9585;
88. Romanos MA, et al., 1991, "Expression of Tetanus Toxin Fragment C in Yeast: Gene Synthesis is Required to Eliminate Fortuitous Polyadenylation Sites in AT-rich DNA," *Nucleic Acids Res.* **19**:1461-1467;
89. Ahnert-Hilger G et al., 1990, "Chains and fragments of tetanus toxin, and their contribution to toxicity" *J Physiol (Paris)* **84**(3):229-236;
90. Andersson SG et al., 1990, "Codon preferences in free-living microorganisms" *Microbial. Rev.* **54**(2):198-210;

91. DasGupta BR et al., 1990, "Botulinum neurotoxin type A: sequence of amino acids at the N-terminus and around the nicking site" *Biochemie* **72**:661-664;
92. Dekleva ML et al., 1990, "Purification and characterization of a protease from *Clostridium botulinum* type A that nicks single-chain type A botulinum neurotoxin into the di-chain form" *J. Bacteriol.* **172**:2498-2503;
93. Thompson DE et al., 1990, "The complete amino acid sequence of the *Clostridium botulinum* type A neurotoxin, deduced by nucleotide sequence analysis of the encoding gene" *Eur. J. Biochem.* **189**:73-81;
94. Wadsworth JDF et al., 1990, "Botulinum Type F Neurotoxin" *Biochem. J.* **268**:123-128;
95. Bittner MA et al., 1989, "Isolated light chains of botulinum neurotoxins inhibit exocytosis. Studies in digitonin-permeabilized chromaffin cells" *J. Biol. Chem.* **264**:10354-10360;
96. DasGupta BR et al., 1989, "C. botulinum neurotoxin types A and E: isolated light chain breaks down into two fragments. Comparison of their amino acid sequences with tetanus neurotoxin" *Biochimie* **71**:1193-1200;
97. DasGupta BR, 1989, "The Structure of Botulinum Neurotoxins" *Botulinum Neurotoxin and Tetanus Toxin*, (Simpson, L.L., Ed.) Academic Press, New York, pp. 53-67;
98. Kozaki S et al., 1989, "Immunological characterization of papain-induced fragments of *Clostridium botulinum* type A neurotoxin and interaction of the fragments with brain synaptosomes" *Infect Immun.* **57**(9):2634-2639;
99. Kozaki et al., 1989, "Antibodies against Botulism Neurotoxin", L.L. Simpson, ed. Academic Press, New York, pp. 301-318;
100. Makoff AJ et al., 1989, "Expression of Tetanus Toxin Fragment C in *E. coli*: High Level Expression by Removing Rare Codons," *Nucleic Acids Res.* **17**:10191-10202;
101. Middlebrook JL, 1989, "Cell Surface Receptors for Protein Toxins" *Botulinum Neurotoxins and Tetanus Toxin*, (Simpson, L.L., Ed.) Academic Press, New York, pp. 95-119;

VOLUME 7

102. Maisy EA et al., 1988, "Involvement of the constituent chains of botulinum neurotoxins A and B in the blockade of neurotransmitter release" *Eur. J. Biochem.* **177**:683-691;

103. Sathyamoorthy V et al., 1988, "Botulinum neurotoxin type A: cleavage of the heavy chain into two halves and their partial sequences" *Arch Biochem Biophys.* **266**(1):142-151;
104. Siegel LS, 1988, "Human Immune Response to Botulinum Pentavalent (ABCDE) Toxoid Determined by a Neutralization Test and by an Enzyme-Linked Immunosorbent Assay" *J. Clin. Microbiol.* **26**:2351-2356;
105. Sreekrishna K et al., 1988, "High Level Expression of Heterologous Proteins in Methylophilic Yeast *Pichia pastoris*," *J. Bas. Microbiol.* **28**:265-278;
106. Winkler HH et al., 1988, "Codon usage in selected AT-rich bacteria" *Biochimie* **70**:977-986;
107. Schagger H et al., 1987, "Tricine-sodium dodecyl sulfate-polyacrylamide gel electrophoresis for the separation of proteins in the range from 1 to 100 kDa" *Anal. Biochem.* **166**:368-379;
108. Shone CC et al., 1987, "A 50-kDa Fragment from the NH₂-terminus of the Heavy Subunit of *Clostridium botulinum* Type A Neurotoxin Forms Channels in Lipid Vesicles," *Euro. J. Biochem.* **167**:175-180;
109. Sonnabend WF et al., 1987, "Intestinal Toxicoinfection by *Clostridium botulinum* Type F in an Adult. Case Associated with Guillian-Barre Syndrome" *Lancet* **1**:357-361;
110. Ahmed SA et al., 1986, "Identification of three sites of proteolytic cleavage in the hinge region between the two domains of the beta 2 subunit of tryptophan synthase of *Escherichia coli* or *Salmonella typhimurium*" *Biochemistry* **25**, 3118-3124;
111. Black JD et al., 1986, "Interaction of ¹²⁵I-botulinum Neurotoxins with Nerve Terminals. I. Ultrastructural Autoradiographic Localization and Quantitation of Distinct Membrane Acceptors for Types A and B on Motor Nerves" *J. Cell Biol.* **103**:521-534;
112. Habermann E et al., 1986, "Clostridial Neurotoxins: Handling and Action at the Cellular and Molecular Level" *Cur. Top. Microbiol. Immunol.* **129**:93-179;
113. Simpson LL, 1986, "Molecular Pharmacology of Botulinum Toxin and Tetanus Toxin" *Annu. Rev. Pharmacol. Toxicol.* **26**:427-453;
114. Cregg JM et al., 1985, "*Pichia pastoris* as a Host System for Transformations," *Mol. Cell. Biol.* **5**:3376-3385;
115. Sathyamoorthy V et al., 1985, "Separation, purification, partial characterization and comparison of the heavy and light chains of botulinum neurotoxin types A, B, and E" *J Biol Chem.* **260**(19):10461-10466;

116. Schmidt JJ et al., 1985, "Partial amino acid sequences of botulinum neurotoxins types B and E" *Arch. Biochem. Biophys.* **238**:544-548;
117. Shone CC et al., 1985, "Inactivation of *Clostridium botulinum* Type A Neurotoxin by Trypsin and Purification of Two Tryptic Fragments. Proteolytic Action Near the COOH-terminus of the Heavy Subunit Destroys Toxin-Binding Activity, *Eur. J. Biochem.* **151**:75-82;
118. Anderson JH et al., 1981, "Clinical Evaluation of Botulinum Toxoids" *Biomedical Aspects of Botulism*, (Lewis, G.E., Ed.) Academic Press, New York, pp. 233-246;
119. Syuto B et al., 1981, "Separation and characterization of heavy and light chains from *Clostridium botulinum* type C toxin and their reconstitution" *J. Biol. Chem.* **256**:3712-3717;
120. Hatheway CL, 1976, "Toxoid of *Clostridium botulinum* Type F: Purification and Immunogenicity Studies" *Appl. Environ. Microbiol.* **31**:234-242;
121. DasGupta BR et al., 1972, "A Common Subunit Structure in *Clostridium botulinum* Type A, B, and E Toxins" *Biophys. Res. Commun.* **48**:108-112;
122. Midura TF et al., 1972, "*Clostridium botulinum* Type F: Isolation from Venison Jerky" *Appl. Microbiol.* **24**:165-167;
123. Laemmli UK, 1970, "Cleavage of structural proteins during the assembly of the head of bacteriophage T4" *Nature* **227**:680-685;
124. van Heyningen WE, 1968, "Tetanus" *Sci. Am.* **218**:69-77;
125. Fiock MA et al., 1963, "Studies of Immunities to Toxins of *Clostridium Botulinum*. IX. Immunologic Response of Man to Purified Pentavalent ABCDE Botulinum Toxoid" *J. Immunol.* **90**:697-702;

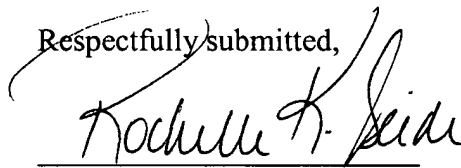
These documents are listed in the accompanying PTO Form 1449. Copies of the documents are submitted herewith.

Identification of the documents listed in the attached PTO Form 1449 is not to be construed as an admission of Applicants or Attorneys for Applicants that such reference is available as "prior art" against the accompanying application.

Applicants have not yet received a first Office Action on the merits. Therefore, Applicants believe that no fee is due with this submission pursuant to 37 C.F.R. §1.97(b)(3). Nevertheless, the Commissioner is authorized to deduct any fee required for this submission from deposit account number 02-4377. Two copies of this page are enclosed.

April 26, 2002

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Rochelle K. Seide", written over a horizontal line.

Rochelle K. Seide
PTO Reg. No. 32,300

Attorney for Applicants
BAKER BOTTS, L.L.P.
30 Rockefeller Plaza
New York, NY 10112
(212) 408-2500

Enclosures